Interference under 37 C.F.R. §1.607, a Showing under 37 C.F.R. §1.608(b) and the Declarations of David Knipe, Robert Finberg, George Siber, Stephen Rice and Min Gao.

The Section 112, first paragraph rejection of claims 1-9, 12-22, 25-27, 29 and 31-41 has been rendered moot with the amendment of claims 1, 5, 9, 12, 17, 18, 25, 32 and 37.

Section 103 Rejection

Claims 1-9, 12-22, 25-27 and 31-41 are rejected as unpatentable over Inglis and further in view of McCarthy and Gao. Applicants submit that in view of the 131 Declaration of David Knipe, which provides evidence establishing conception and reduction to practice of a vaccine comprising herpesvirus replication defective mutant which provides a protective immune response, prior to the effective date of Inglis, whereby Inglis is removed as prior art.

David Knipe is the sole inventor of the subject matter of claims 9, 25-41, and new claims 42-49. The subject matter of these claims was originally described in U.S. application serial no. 07/922,912, filed July 31, 1992, now abandoned, in which David Knipe was named as sole inventor. Robert Finberg and George Siber were named as co-inventors in the above-captioned application as a result of their inventive contribution with respect to a composition and method for treating an immunomodulatory disease by use of a mutated herpesvirus that has an ability to effect an antibody shift, and induce IFN-gamma production. This is the subject matter of claims 1-8 and 12-22.

Applicants submit that subject matter of the invention of claims 9, 25-41 and 42-49 is patentable over Inglis because applicants conceived and reduced the invention that is the subject matter of claims 9, 25-41 and 42-49 to practice prior to the effective date of Inglis of April 2, 1992. Further, claims 9, 25-41 and 44-49 disclose both the genus and a species of replication defective mutant herpesviruses.

Applicants provide evidence of this prior conception and reduction to practice in the form of a 131 Declaration of the Inventor, David Knipe, that in the United States prior to April 2, 1992

an ICP27 mutant herpesvirus that was replication defective was conceived and reduced to practice as follows:

An ICP27 gene nonsense codon insertion mutant herpesvirus n504R was propagated and titrated on V-27 cells. V-27 cells can produce the mutant herpesvirus because they contain an integrated copy of the ICP27 gene, thus they complement the growth of HSV-1 ICP27 mutants and serve as hosts for the isolation of ICP27 mutants. A replication defective mutant such as n504R will not however replicate on normal cells such as Vero cells which are routinely used for growth of HSV-1, since they lack an ICP27 gene.

V-27 cells were infected with an n504R mutant herpesvirus. After harvesting the propagated herpesvirus from the cells, the n504R mutant herpesvirus was aliquoted and frozen at –70 and designated "M28 n504R". A sample of the virus was tested for its ability to replicate by measuring plaque formation in cells infected with the mutant herpesvirus. The mutant herpesvirus n504R was tested for plaque formation on V-27 cells and on Vero cells. The results showed that the n504 mutant herpesvirus failed to produce plaques on the Vero cells at the lowest dilution (10^{-3}) that could be read (lower dilutions killed the monolayer). At that same low dilution the V-27 cell monolayer had too many plaques to count. Distinct and measurable plaques were formed on the V-27 cells at much higher dilutions tested in the V-27 cells (10^{-7}). A virus titer of 4×10^{8} was calculated. These results confirmed that n504R is a replication defective ICP27 mutant herpesvirus.

Applicants also provide evidence in the Declaration of David Knipe that in the United States prior to April 2, 1992 an ICP8 mutant herpesvirus that was replication defective was conceived and reduced to practice as follows:

An ICP8 gene internal deletion mutant herpesvirus d301 was propagated and titrated on S-2 cells. S-2 cells can produce the mutant herpesvirus because they express the ICP8 protein from a resident gene upon viral infection, thus they provide the complementing gene product that the mutant protein is missing. A

replication defective mutant such as d301 will not however replicate on normal cells such as Vero cells which are routinely used for growth of HSV-1, since they lack an ICP8 gene.

S-2 cells were infected with d301 mutant herpesvirus. After harvesting the propagated virus from the cells, the virus was tested for its ability to replicate by measuring plaque formation in cells infected with the mutant herpesvirus. The mutant herpesvirus ICP8 d301 was tested for plaque formation on S-2 cells and on Vero cells. The results showed that the d301 mutant herpesvirus failed to produce plaques on the Vero cells, even at the lowest dilution tested (10^{-2}). At that same low dilution the S-2 cell monolayer was destroyed by the d301 mutant herpesvirus. At much higher dilutions (10^{-7}) distinct plaques were formed on the S-2 cells, were counted and a viral titer of 1.7×10^{9} was calculated. These results confirmed that d301 is a replication defective ICP8 mutant herpesvirus. The d301 mutant herpesvirus was aliquoted and designated "d301.a _____" stock.

Applicants further provide evidence in the Declaration of David Knipe that in the United States prior to April 2, 1992 the two mutant herpesviruses provided a protective immune response in animals to challenge with wild type herpesvirus and was reduced to practice as follows:

10^{6} pfu of replication-defective viruses, those containing mutations in the genes encoding ICP8 or ICP27, were injected into mice, and then challenged with a lethal dose of 10^{8} pfu live wild-type HSV-1 virus. The mice that received the mutants had 100 % survival rates whereas the control mice that did not receive mutant virus had a 10 % survival rate. Thus the experiments demonstrated that replication defective mutants of HSV-1 induced immunity in mice injected with the mutant viruses and protected against lethal infection whereas the majority of mice injected with control material and subsequently challenged with wild type virus, died.

Thus, the accompanying Declaration under Rule 131 demonstrates that the invention of claims 9, 25-41, and new claims 42-49 was conceived and reduced to practice prior to the effective date of Inglis. Since the primary reference has been removed, claims 9, 25-41, and new claims 42-49 are patentable over the prior art.

Applicants' replication defective herpesvirus species ICP8 and ICP27 are patentable over Inglis' mutant herpesvirus species glycoprotein H.

The infection of susceptible cells with herpesvirus includes transcription, replication of viral DNA, assembly of new virus particles or capsids and transportation of the infective capsids to other cells. A mutation in a herpesvirus gene that will prevent any of these steps from occurring will be considered to prevent production of new infectious.

Applicants have shown that with their replication defective herpesvirus the virus does not replicate in the cell into which the virus is placed as evidenced by lack of plaque formation. The mutant viruses will not produce new virus or new viral particles therefore there is no production of infectious virus in new cells.

The invention of Inglis et al comprises mutation in a gene of an essential protein required for transport of new viral particles into new cells. Both Inglis and applicants have shown that their mutant herpesviruses cannot infect new cells. The viral mutants of both inventions have the ability to enter a cell initially, and both are incapable of infecting other cells in turn. Thus both inventions are encompassed by the same genus.

However, the two inventions render the viruses non-infective in completely different ways. The mutant of Inglis et al can infect a cell initially, can replicate its genome normally and can package viral particles, but cannot make a protein required for the viral infection of new host cells and thereby producing non-infectious progeny. Therefore Inglis has affected the ability of the virus to infect normal cells by mutating an essential protein involved in a post-replicative event.

The mutants of a preferred embodiment of the present invention, on the other hand, are incapable of producing additional virus. In the present invention, an essential protein involved in a replicative event is mutated; unlike the mutants of Inglis, they cannot create new particles. Thus the two inventions comprise two different species of the same generic invention.

Although Inglis suggests the production of a herpesvirus having a mutation in a gene involving viral genome replication (col.3, lines 38-39), applicants have shown actual reduction to practice of a species of a replication defective mutant herpesvirus prior to the effective filing date of Inglis. Therefore, insofar as Inglis discloses a gene for replication defective virus, applicants have provided evidence that they have conceived and reduced to practice subject matter that is patentable over the generic count which broadly encompasses the non infectious virus of both applicants and Inglis.

Applicants species are patentable over Inglis' species

Applicants invention comprises a mutation in a gene of an essential herpesvirus protein required for infectivity of the virus in normal cells. Applicants disclose the mutations of genes expressing proteins essential for the expression of later expressed herpesvirus genes. HSV-1 genes are expressed in four sequential classes α (immediate early), β (early), γ^{-1} and γ^{-2}. The expression of the β and γ classes of genes requires the expression of functional α proteins. ICP27 gene is an α gene and thus a malfunction in this gene affects the expression of later expressed proteins γ^{-1} and γ^{-2}. ICP8 is the product of a β gene and is required for viral DNA synthesis and normal regulation of viral gene expression. A mutation in either of these genes will result in a failure to express these proteins and no replication of the viral genome. Yet as applicants have shown, the viruses so mutated surprisingly provide a protective immune response against infection.

Inglis, on the other hand, provides a viral mutant wherein the glycoprotein gH is inactivated. HSV-1 glycoproteins such as gH are involved in post viral replication events, thus most of the early or intermediate proteins have been expressed. Inglis teaches that the deletion

of a late expressed protein will allow maximum production of earlier expressed proteins to generate a maximum immunogenic response.

> "The deleted or inactivated gene is preferably one involved as late as possible in the vital cycle, so as to provide as many vital proteins as possible in vivo for generating an immunologic response. For example, the gene may be one involved in packaging or some other post-replicative event such as the gH glycoprotein of HSV." (U.S. Pat. No. 5,665,362, col. 3 lines 33-38; also col. 4 lines 5-21).

Thus, it would not be obvious from the teachings of Inglis that deactivation of an early intermediate HSV-1 gene would result in a herpes mutant virus which would provide an adequate protective immune response. It could not be reasonably predicted that such a mutated virus would be suitable for use as a vaccine in that Inglis would lead one skilled in the art to expect that mutation of an early gene would reduce immunogenicity (see Inglis col 3 lines 33-36). One of skill in the art would not be able to reasonably predict that such a mutant herpesvirus would generate a sufficient immunogenic response to generate protective antibodies.

McCarthy is concerned solely with the study of the role of ICP27 in HSV gene expression. McCarthy does not suggest using the particular mutants examined in the study of the interrelationship with early and late gene expression for any other purpose, or for any other gene. McCarthy does not provide the necessary element of utilizing ICP27 gene mutants as vaccines McCarthy do not discuss the possibility of using such mutants as vaccines.

Gao, (referred to by the Examiner as Guo), relates to studies of the ICP8 gene and its function in nuclear localization and DNA-binding. Gao does not suggest using the ICP8 gene for the purpose of vaccines. Neither reference provides the suggestion or motivation to combine references. Taken together therefore the combination does not make obvious the use of a mutant virus as a vaccine since nowhere do they suggest how to apply their teachings to vaccine development.

In order to combine references there must be some teaching for supporting the combination under a Section 103 rejection. *In re Lalu and Foulletier* 223 USPQ 1257, 1258 (Fed. Cir. 1984). As discussed above, neither McCarthy nor Gao provide such a teaching.

Further, neither reference suggests that using any of the herpesvirus mutants described therein will be likely to succeed in being useful as a vaccine. For a Section 103 rejection to stand, the prior art must provide a reasonable expectation of success of producing the claimed invention. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d1016, 1022 (Fed.Cir. 1991).

Applicants submit that Inglis has been removed as a Section 103 reference. As discussed above, the secondary references do not make the claimed invention obvious.

Allowable claims

Applicants point out that claims 4, 8, 15, 21, 27, 29, 35 and 40, which had been solely rejected under Section 103, and are directed to particular species ICP8 and ICP27, are now allowable because Inglis has been removed as prior art. New claim 49 also directed to specific mutants ICP8 and ICP27, is believed to be also allowable.

Claims 1-8 and 12-22

Claims 1-8 and 12-22 are directed to a composition and method for treating an immunomodulatory disease by use of a mutated herpesvirus that has an ability to effect an antibody shift, and/or induce IFN-γ production. Applicants submit that Inglis is not pertinent prior art with regard to these claims. There is clearly no suggestion in Inglis or the other cited references to generate replication defective herpesviruses in order to effect an antibody subclass shift of IgG2a/IgG or induce production of IFN-γ, or that such mutant virus may be used for treating an immunomodulatory disease. Thus, applicants respectfully submit that claims 1-8 and 12-22 are patentable over the prior art.

Section 112 Rejection

Claims 1-3, 5-7, 9, 12-14, 16-20, 22, 25, 26, 31, 32, 33, 34, 36, 37-39 and 41 are rejected under 35 U.S.C. §112 as the full scope of the claimed invention is allegedly not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner supports the rejection by asserting that the specification only discloses two genes, ICP8 and ICP27. The Examiner further asserts that herpesvirus proteins differ in structure, therefore undue experimentation would be required to practice the broad scope of the invention.

Firstly, applicants have described, in detail, construction and characterization of the claimed mutant herpesviruses having a mutation in genes encoding a protein for viral replication which renders the herpesvirus replication defective (specification pp. 16-40). Applicants demonstrated that the ICP8 mutant was unable to replicate in Vero cells and required complementation by the wild type copy of the ICP8 gene (pp. 34-35). Furthermore, applicants teach and have demonstrated how to use the replication defective viruses as a vaccine. Routes of administration are discussed at page 15. Applicants have shown that upon administration to a mammal, the replication defective herpesviruses induce an immunological protective effect (pp. 40-46 and 55-61).

Secondly, applicants review in a comprehensive manner the prior art and what is known about herpesviruses. One of skill in the art at the time of the invention had an abundance of information at hand regarding the genomic sequences of herpesviruses, such as HSV-1, VZV, EBV and CMV (see specification and cites therein, page 7 lines 2-18) and essential genes (page 8). Herpesviruses are homologous (e.g. see page 9 HSV-1 and HSV-2 are homologous) and the corresponding proteins in herpesviruses other than HSV-1 or HSV-2 can be mutated to obtain a replication defective mutant virus (see specification page 8 lines 27-21 and 29-page 9 line 19). Davison et al. observed that herpesviruses varicella-zoster virus (VZV)and HSV-1 possessed several conserved genes arranged colinearly in the genomes (Davison A.J. et al.; *J. Gen. Virol. 67*:1759-1816 (1986) cited at page 7). Davison confirmed this finding upon sequencing the entire DNA sequence of VZV and concluded that a majority of corresponding genes were functionally similar. Chee et al. (*Current Topics in Microbiol. and Immunol.154*:125-169 (1990) cited at page 7) disclosed obvious homologies between CMV and HSV-1. The function of the proteins of the Epstein-Barr virus have also been predicted based upon sequence homology with

HSV-1 (Baer et al. *Nature 310*:207 (1984) cited at page 7). Applicants have already made these publications of record.

Applicants submit that the viruses described in the specification and in the prior art are homologous and have certain common predictable characteristics. More importantly, "essential genes", by definition, have at least one common property which is required for the present invention and that is the gene is required for the production of new virus in a host cell, that is, the protein is essential for replication. Then, by definition its inactivation, either by mutation or deletion, will render the mutant virus replication–defective. Applicants describe the desired characteristics of a viral mutant for purposes of the present invention, *e.g.* on page 8: "A replication defective virus can be obtained by-effectively mutating the gene or genes encoding one or more proteins required for completing the replication cycle"; on page 10, the replication defective mutants include "any viral mutant which is viable, is incapable of replication and elicits a protective immune response or an immunomodulation."; on page 11: "virus specific products generally responsible for eliciting a protective immune response are proteins and glycoproteins".

The specification verifies the assertion that a mutation in an essential gene renders the virus replication defective by showing that inactivation of three essential genes, ICP4, ICP8 and ICP27, resulted in functional mutant viruses. Thus, one of skill in the art would reasonably expect that inactivation of other essential genes would produce a virus that could not replicate.

The person of skill in the art is taught by the prior art that herpesvirus genes have homology; the person of skill in the art also finds significant guidance in the present specification to obtain replication defective mutants in HSV-1 and HSV-2. Thus, the person of skill in the art is more than sufficiently enabled to practice the breadth of the claimed invention.

The first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the used of illustrative examples or by broad terminology is of no importance. *In re Marzocchi and Horton* 169 USPQ 367, 369(CCPA 1971)

Applicants provide both detailed illustrative examples and review what is known in the prior art to teach and enable the practice of the full scope of the claimed invention.

Representative examples of all viruses are not required to enable the present invention. Such a requirement would put undue burden on the applicants to carryout a thousand of experiments and stifle the patent process. Such a disclosure is not required even in an unpredictable art *In re Angstadt and Griffin* 190 USPQ 214 CCPA (1976). Applicants are not required by the law to discover which of all possible viral genes will function properly. *In re Fuetterer* 138 USPQ 217, 223 (CCPA 1963).

The Examiner also asserts that the specification does not provide sufficient guidance to practice the present invention because the specification discloses herpesvirus mutants that do not have the claimed properties. Firstly, a disclosure of an example that does not yield the desired result does not make the disclosure nonenabling under patent law. Disclosure of operative as well as inoperative examples is considered to be well within the parameters of scientific inquiry. (see *In re Angstadt*):

> "Such variation of treatment must be within the scope of the claims, and *the certainty which the law requires in patents is not greater than is reasonable...*" *In re Angstadt* at 219 citing *Minerals Separation Ltd v Hyde* 242 U.S. 262, 270-71(1916).

In *Angstadt,* the court found that appellants' disclosure was fully enabling even though the particular process was in an unpredictable art and the appellants disclosed several examples out of many that were inoperable.

> "We hold that the evidence as a whole including the inoperative as well as the operative examples, negates the PTO position that persons of ordinary skill in this art, given its unpredictability, must engage in undue experimentation to determine which complexes work." (*In re Angstadt* at 219)

Thus, even if Applicants did provide examples of viral mutants that did not have the claimed properties, given the teachings in the specification and the voluminous amount of information available to those of skill in the art regarding herpesvirus, the specification fully enables the scope of the invention as claimed.

The example pointed out by the Examiner involves the ICP4 deletion mutant and its failure to induce an antibody subclass shift. However, applicants teach that the ICP4 deletion mutant is replication defective and that the above result is likely due to that fact that the ICP4, ICP8 and ICP27 proteins vary in their function and regulation of expression of α β and γ genes and conclude:

> "Thus, specific components of the viral replication cycle, and not production of infectious progeny virus, are required for induction of the subclass shift." (page 51)

Thus, applicants provide further guidance to those of skill in the art as to how to select the appropriate essential gene to obtain a herpesvirus mutant having the desired properties.

Applicants point out that only claims 1-4 and 12-22 are directed to a mutant herpesvirus that induces an antibody subclass shift. Even if the Examiner's argument, that a "negative" result renders an invention nonenabled, was valid, it would not be applicable to the other claims under rejection.

Applicants submit that they have fully complied with the requirements of Section 112. Applicants have provided a written description of the invention and the manner and process of making it in full, clear concise and exact terms to enable a person of skill in the art to make and use the claimed invention.

As the court said in *In re Marzocchi*:

> "As a matter Patent Office practice then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless that is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. " (at 369).

Applicants having met their requirement, the burden is now on the Patent Office to provide substantiated reasons as to why it doubts the truth of the statements made in the disclosure.

> "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure

> and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." (*In re Marzocchi* at 370)

The Examiner has not provided any reasoning or scientific evidence to support his assertion that because herpesviruses differ in structure, undue experimentation would be required to practice the invention as claimed.

Inglis

Applicants point out that applicants' claims 42 and 43 substantially correspond to claim 1 of U.S. Patent No. 5,665,362, of Inglis, which corresponds to WO92/05263 of Inglis cited against applicants in the above captioned application in the Office Action. Claim 1 of Inglis is directed to a vaccine comprising a mutant herpesvirus wherein a gene essential for production of infectious virus has been mutated, such that the virus will not cause production of new virus.

Inglis discloses viral genomes of various viruses and discloses several essential genes. However, Inglis only provides one working example of the mutation of one essential herpesvirus protein, glycoprotein H, which protein is involved in a post-replicative event. Inglis' originally filed claims were subject to a Section 112 first paragraph enablement rejection, similar to the rejection of applicants' claims in the present application.

A review of the Inglis file history reveals that extensive reviews of the prior art knowledge regarding viruses were presented, including a Declaration of the inventor Dr. Inglis, wherein Dr. Inglis identified a large number of known essential genes, many of which were known to have homologs in other herpes viruses. It appears that in view of these disclosures, and in view that Inglis narrowed the scope of the originally filed claims to encompass only herpesvirus, the Patent Office deemed the claim directed to any mutant herpesvirus/any essential gene to be patentable, even though Inglis exemplified the production of only one mutant herpesvirus having a mutation in the herpesvirus glycoprotein H gene. The Patent Office apparently did not doubt the truth of the assertions made by Inglis with respect to the scope of his claims as to all herpesviruses.

Applicants have provided background information commensurate with that provided by Inglis. Applicants have further exemplified three mutant herpesvirus vaccines. Although Inglis provided exemplification of only one essential gene mutation, the glycoprotein H gene, a claim encompassing any mutant herpesvirus that does not produce infectious virus was issued.

Conclusion

Applicants submit that the invention as claimed is enabled based on applicants' teachings in the specification and the considerable amount of information existing in the prior art that identified essential genes in a variety of viruses and particularly herpes viruses.

Thus, as the Patent Office has failed to provide sufficient grounds for a rejection based on Section 112, and applicants have provided an enabling specification, applicants respectfully request that the Section 112 rejection of claims 1-3, 5-7, 9, 12-14, 16-20, 22, 25, 26, 31, 32, 33, 34, 36, 37-39 and 41 be withdrawn.

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